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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,624	10/26/2001	Keith D. Allen	R-666	1008

7590 04/16/2004

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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,624	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-42 have been cancelled. New claims 43-50 have been added. Claims 43-50 are pending and are under current consideration.

Upon further consideration the following new grounds of rejection are necessary:

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 43-50 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are directed to a transgenic mouse whose genome comprises a homozygous disruption in an endogenous TSH-R gene, wherein the mouse exhibits reduced growth and development, relative to a wild-type mouse. The claims are further directed to methods of making and using the same transgenic mouse.

The instant specification has contemplated that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a thyroid stimulating hormone receptor. The instant specification has further contemplated that disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in a mouse will produce a phenotype related to a thyroid stimulating hormone receptor. The instant specification has purported that such mice

may be used to identify agents that modulate or ameliorate a phenotype associated with a disruption in SEQ ID NO: 1.

The instant specification has disclosed a transgenic mouse whose genome comprises a disruption in SEQ ID NO: 1, wherein the mouse exhibits dwarfism; hunched posture; small eyes and ears; small thymus gland; a malformed femur; small skeletal muscle; decreased fat in the subcutis; small or not visible seminal vesicles; low body weight; short body length; low organ weight (spleen, liver, kidneys, heart, thymus); low organ weight to body weight ratio (spleen, liver, kidneys); small thyroid gland with small follicles; abnormalities of the pituitary gland consisting of adenohypophysis, large and vacuolated cells, reduced chromophils, pars distalis, and chromophobe hypertrophy; dysplasia of the epiphyses of the femur, tibia and stifle joint; reduced patchy ossification of bones; reduced cellularity of bone marrow; hypoplasia with absence of cortico-medullary distinction of the thymus gland; immature kidneys with small glomeruli, lymphocytic infiltrates in the kidneys; immature testes; hypospermatogenesis; insterstitial Leydig cell hyperplasia; oligospermia; lymphocytic infiltrates in the lungs; diffuse retinal fibrosis and elevated blood urea nitrogen. The claims embrace such a mouse and a method of making the mouse. The instant specification has discussed that phenotypes exhibited by such a transgenic mouse could correlate to a disease or disorder. However, the evidence of record does not provide a correlation between the disclosed phenotypes (as recited above) and any disease or disorder. Moreover, while the specification has purported that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a thyroid stimulating hormone receptor, the evidence of record has failed to

provide a correlation between any thyroid stimulating hormone receptor related disease/disorder and the disclosed phenotypes. The specification has provided general assertions that the claimed transgenic mice may be used to identify agents that affect a phenotype related to the mice.

As such, the asserted utility, for the transgenic mouse embraced by the claims, of screening agents that may affect a phenotype of said mouse as provided by the instant specification and encompassed by the claims, does not appear to be specific and substantial. The asserted utility does not appear specific and substantial to the skilled artisan since the evidence of record has not provided any suggestion of a correlation between any thyroid stimulating hormone receptor, the disclosed phenotypes exhibited by the transgenic mouse, and any disease or disorder. Since the evidence of record has not provided a correlation between the disclosed phenotypes and any disease or disorder, the utility of identifying agents that affect such phenotypes is not apparent. The evidence of record has not provided any other utilities for the transgenic mouse embraced by the claims that are specific, substantial, and credible.

The asserted utility of the transgenic mouse embraced by the claims is based on the expectation that disrupting the nucleotide sequence set forth in SEQ ID NO: 1 would result in a detectable phenotype in the mouse. The phenotypes observed in the transgenic mice embraced by the claims are dwarfism; hunched posture; small eyes and ears; small thymus gland; a malformed femur; small skeletal muscle; decreased fat in the subcutis; small or not visible seminal vesicles; low body weight; short body length; low organ weight (spleen, liver, kidneys, heart, thymus); low organ weight to body

weight ratio (spleen, liver, kidneys); small thyroid gland with small follicles; abnormalities of the pituitary gland consisting of adenohypophysis, large and vacuolated cells, reduced chromophils, pars distalis, and chromophobe hypertrophy; dysplasia of the epiphyses of the femur, tibia and stifle joint; reduced patchy ossification of bones; reduced cellularity of bone marrow; hypoplasia with absence of cortico-medullary distinction of the thymus gland; immature kidneys with small glomeruli, lymphocytic infiltrates in the kidneys; immature testes; hypospermatogenesis; insterstitial Leydig cell hyperplasia; oligospermia; lymphocytic infiltrates in the lungs; diffuse retinal fibrosis and elevated blood urea nitrogen . While the phenotypes exhibited by the claimed transgenic mouse are contemplated to be associated with a disease, the association of such phenotypes with any disease has yet to be elucidated. In fact the art suggests that phenotypes exhibited by knockout mice, are greatly influenced by the genetic background of the tested mouse. For example, Schuster-Gossler et al (Mammalian Genome, 1996, 7: 20-24) observe that a dwarfism phenotype in offspring is affected by the sex of the parent from which the transgene is inherited and also by the genetic background of the mice. See throughout the entire document. Furthermore, Schoor et al (Mechanisms of Development, 1999, 85: 73-83) discuss that phenotypes of retarded growth, peri/post natal lethality, reduced fertility, and skeletal abnormalities are influenced by the genetic background of the knockout mouse. See throughout the entire document.

Therefore, the reference suggests a need to provide independent evidence of an association of the disclosed phenotypes exhibited by the transgenic mouse embraced

by the claims with a disease or disorder. However, neither the specification nor any art of record provides evidence of the existence of a correlation between such phenotypes and a disease or disorder, leaving the skilled artisan to speculate and investigate the uses of the transgenic mouse embraced by the claims. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the transgenic mouse embraced by the claims. In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse embraced by the claims to be specific and substantial.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-50 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, the following rejections are maintained from the previous enablement rejection:

The aspect of the previous enablement rejection relating to phenotypes of transgenic knockout mice is maintained for the reasons of record advanced on pages 8-10 of the Office action mailed on 9/26/03.

Applicant's arguments filed 1/30/04 have been fully considered but they are not persuasive. Applicants contend that the pending claims now recite a homozygous transgenic mouse exhibiting a phenotype of reduced growth and development resulting from disruption of a TSH-R are fully enabled and described by the instant specification.

In response, the Examiner asserts the pending claims are not fully enabled for phenotypes resulting from disruption of any TSH-R gene. Rather, the phenotypes recited in the claims result from disruption of the nucleotide sequence set forth in SEQ ID NO: 1. It is further maintained that phenotypes resulting from disruption of a gene are unpredictable as set forth in the previous Office action. See Moreadith and Moens on pages 8-9 of the Office action mailed on 9/26/03. Also see Leonard et al (Immunological Reviews, 1995, pages 97-114) who discuss that inactivation of the gene encoding cytokine receptor γ chain in transgenic mice results in a phenotype different from that expected. The recited phenotypes are specific only for disruption of the nucleotide sequence set forth in SEQ ID NO: 1 and not for disruption of any TSH-R gene. Also, the breadth of the phenotypes recited in claim 43 is not fully enabled by the guidance provided by the instant specification. The claim recites phenotypes of reduced growth and development. However, the breadth of such encompasses any growth or developmental abnormality while the specification has only disclosed specific growth or developmental abnormalities resulting from disruption of the nucleotide sequence of SEQ ID NO: 1. As discussed above, phenotypes resulting from disruption of a gene are unpredictable.

Accordingly, the aspect of the previous enablement rejection relating to unpredictability of phenotypes resulting from disruption of a gene is maintained for the reasons of record.

The aspect of the previous rejection relating to embryonic stem cells has been withdrawn in light of the newly presented claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is (571) 272-0732. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS, JR.
PRIMARY EXAMINER